REMARKS

Claim Amendments

Applicants have amended claims 1, 12 and 14 to further specify the characteristics of the hematologic malignancies that are to be treated according to the claimed method. The claim amendments specify that the hematologic malignancy is one that has high levels of circulating tumor cells, which are identified by measured levels of white blood cells in the range from about 4 X 10^9 white blood cells per liter to about 200 X 10^9 white blood cells per liter of blood. Support for this amendment is found in Applicants' specification at page 1, lines 5 to 8, page 2, lines 15 to 17, page 3, lines 13 to 17, and, *inter alia*, Example 3. Claim 11 has been amended to correct an obvious typographical error.

Applicants have amended claims 7 and 17 to delete the trademark "RITUXAN®" from these claims, and to use only the term "rituximab" in these claims. .

Related Applications

Applicants wish to bring to the attention of the Examiner the following co-pending applications: 09/628,187, 09/783,038, 09/911,703, 09/911,692, 09/905,928, 10/096,964, 08/921,060, 10/238,681, 10/196,732, and 10/440,186.

Information Disclosure Statement

Applicants request the Examiner to consider the enclosed Information Disclosure Statement.

35 U.S.C. §112 Rejection

The Examiner has maintained the rejection of claim 7 under 35 U.S.C. §112, first paragraph. The Examiner has urged that the application does not contain complete evidence

either that the claimed biological materials are known or readily available to the public, or that there has been a proper deposit of the biological materials. The Examiner maintains that only the variable region sequences have been disclosed.

The Examiner's attention is directed to the disclosure of the full-length amino sequence and the corresponding nucleic acid sequence of anti-CD20 in U.S. Patent No. 5,736,137 to Anderson et al., col. 31-54. The contents of the '137 patent are expressly incorporated by reference in the specification of the present application at page 6, lines 6-17 of the Applicants' specification. Applicants further note that the nucleic acid comprising an anti-CD20 antibody in the TCAE 8 expression vector was deposited with the ATCC incidental to the '137 patent. See, Column 32, lines 12 to 27, which provide as follows:

> VI. DEPOSIT INFORMATION
>
> Anti-CD20 in TCAE 8 (transformed in *E. coli* for purposes of deposit) was deposited with the American Type Culture Collection (ATCC) on Nov. 4, 1992, 12301 Parklawn Drive, Rockville, Md., 20852, under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure ("Budapest Treaty"). The microorganism was tested by the ATCC on Nov. 9, 1992, and determined to be viable on that date. The ATCC has assigned this microorganism for the following ATCC deposit number: ATCC 69119 (anti-CD20 in TCAE 8). Hybridoma 2B8 was deposited with the ATCC on Jun. 22, 1993 under the provisions of the Budapest Treaty. The viability of the culture was determined on Jun. 25, 1993 and the ATCC has assigned this hybridoma the following ATCC deposit number: HB 11388.

Applicants note that this nucleic acid was deposited in the form of a transformed *E. coli* cell line containing the Anti-CD20 in TCAE 8 nucleic acid. Applicants submit that the disclosure of the nucleic acid sequence of, *inter alia*, rituximab clearly establishes sufficient written description for the antibodies used in the claimed method, and that this sequence was both in the form of the textual description in the '137 patent and in the form of a deposit of the sequence in the above-noted transformed *E. coli* cell line.

Applicants also observe that the deposit made with the ATCC referenced in the above-quoted portion of the '137 patent is fully responsive to the concerns raised by the Examiner. Applicants enclose herewith a copy of a letter from the ATCC, evidencing confirmation by the ATCC that patent deposits assigned ATCC No. HB-11712 and ATCC No. 69119 have been released for public distribution and are currently available for order. A copy of this letter was previously submitted with Applicants' Amendment on January 29, 2004.

In view of the above, the Examiner is requested to withdraw the rejection of claim 7 on the basis of a lack of adequate written description of the invention.

The Examiner has also rejected claims 1, 12, 13 and 19-27 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. The Examiner urges that Applicants' amendment of claims 1, 13, 14 and introduction of new claims 19-27 reciting the phrase "at least about 40 x 10^9 white blood cells per liter" constitutes new matter. The Examiner acknowledges the Applicants' specification at pages 12-13 provides a teaching of an example of a patient with high levels of circulating tumor cells characterized, in particular, by a white blood cell count ranging from about 4 x 10^9 to 200 x 10^9 white blood cells per liter of blood.

The present amendments address the basis of the Examiner's rejection by specifying that the hematologic malignancy being treated according to the claimed method is one that is characterized by a white blood cell count ranging from about 4×10^9 to 200×10^9 white blood cells per liter of blood. The white blood cell count range specified in the claims is known in the art as being one factor indicative of the presence of the types of hematologic malignancies that are the subject of the claimed method, such as CLL. See, e.g., *Byrd et al.*, J. Clin.Onc., 17:3, 791 (1999). The types of hematologic malignancies that are the subject of the claim are also easily identified through inspection of the specification. For example, the specification identifies a number of specific types of hematologic malignancies that are those with high levels of circulating tumor cells in the blood. See, e.g., the sentence bridging pages 2 and 3 ("Examples of such hematologic malignancies include B-pro-lymphocytic leukemia (B-PLL) chronic lymphocyte leukemia (CLL and transformed non-Hodgkin's lymphoma)").

Applicants submit that the claim amendments made in the present amendment have full support from the specification, and do not constitute new matter. For example, Applicants note that in Example 3 of the specification, at pages 12 to 13, the patient treated in accordance with the claimed method was diagnosed with CLL *inter alia* because the patient had a white blood cell count of 40×10^9, and white blood cell count range from about 4×10^9 to about 200×10^9 white blood cells per liter of blood.

In view of the amendments made by the present response, Applicants submit that the claimed subject matter is fully supported by the specification and is not directed to any new matter. Accordingly, the Examiner is respectfully requested to withdraw the rejection of these claims on this basis.

The Examiner also has rejected claim 7 as vague and indefinite in the recitation of RITUXAN®. Applicants have deleted the trademark from claims 7 and 17. Accordingly, the Examiner is requested to withdraw this rejection.

35 U.S.C. §102 Rejection

The Examiner has rejected claims 1-4 and 7-27 under 35 U.S.C. 102(e) as anticipated by US Patent No. 6,455,043 (effective filing date August 11, 1998) (hereafter "the '043 patent"). The Examiner urges that the '043 patent discloses a method of treating patients with a variety of B-cell lymphomas, including chronic lymphocytic leukemia and high grade lymphoblastic non-Hodgkin's lymphoma with an anti-CD20 antibody (abstract and col. 2, line 1-col. 4, line 54). The Examiner further urges that the anti-CD20 antibody could be chimeric, humanized, radiolabeled and preferentially is C2B8; that it teaches treating CLL patients with a medium white blood cell count of 40 x 10^9 per liter; and that combination therapy can be administered. The Examiner further urges that there is disclosure of several means of performing the disclosed methodology and that infusion resulted in a reduction in peripheral blood lymphocytosis, which renders a reduction in circulating tumor cells. The patent discloses that the method "will be particularly useful for patients who are refractory . . . after treatment with chemotherapeutic drugs."

Claim 1, as amended, relates to a method of treating a hematologic malignancy characterized by the presence in the patient of a white blood cell count within a range of from about 4 x 10^9 white blood cells per liter to about 200 x 10^9 white blood cells per liter of blood wherein the method comprises administering a therapeutically effective amount of an anti-CD20 antibody or antigen-binding fragment thereof, said amount being effective to achieve a reduction in circulating tumor cells. The §102(e) prior art effect of a patent depends on whether the patent

claims the benefit of any earlier filed application. If the patent does claim such priority, the priority document controls the question of anticipation under §102(e) with respect to anticipation as from the priority date (as opposed to the actual filing date of the non-provisional application that leads to the patent). To anticipate under §102(e) as from the priority date, the priority application must disclose each and every limitation of the claimed invention.

Here, the '043 patent claims the benefit under 35 U.S.C. §119(e) to a provisional application (60/096,180). The priority date of the present application is later than the priority date of the '180 provisional application, but earlier than the actual filing date of the non-provisional application that led to the '043 patent. The '180 provisional application does not literally disclose treatment of patients presenting with circulating white blood cell counts in the range specified in the amended claims. On this basis, the '043 patent does not anticipate, under §102(e), the newly amended claims.

Accordingly, Applicants respectfully request the Examiner to withdraw the rejection of the claims over the '043 patent.

35 U.S.C.§103 Rejection

The Examiner has rejected claims 1-27 under 35 U.S.C. §103(a) as unpatentable over the '043 patent. The Examiner acknowledges that the patent does not teach the administration of the antibody at a dosage ranging from 0.1 to 30 mg/kg weekly for about 2 to 10 weeks. The Examiner urges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the anti-CD20 antibody in the recited dosages at the designated time points. The Examiner maintains that one of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art, and urges that the dosages of any therapeutic agent must be adjusted and

optimized. The Examiner further urges that the patent provides the impetus for one of ordinary skill in the art to optimize and implement varying dosages in order to identify a useful treatment regimen because, in several instances (col. 13, lines 14-17, lines 31-33 and 52-58), the '043 patent suggests several administration plans. Applicants note that the Examiner has rejected claims 1-27 on this basis but has cited the limitations of claims 5 and 6. As the Examiner's rejection is based upon the dosage ranging from 0.1 to 30 mg /kg weekly for about 2 to 10 weeks, Applicants understand the rejection to be directed to claims 5 and 6. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the present claims define a process that is not obvious under §103 from the cited prior art. To properly reject a claim as obvious under §103, the Examiner must present evidence and arguments that establish a *prima facie* showing that the claimed invention is obvious over the prior art. The Examiner's *prima facie* showing must address the specific limitations in the claims, and in particular, identify those distinctions from the prior art that, despite establishing the invention is not anticipated, would nonetheless, in the opinion of the Examiner, render the claimed invention obvious under §103.

In the last Office Action, the Examiner maintained rejections under §103 of the claimed invention over the '043 patent. The Examiner acknowledged that the patent does not literally disclose the administration of an antibody "at a dosage ranging from 0.1 to 30 mg/kg weekly for about 2 to 10 weeks." See, page 8, paragraph 15 of the last Office Action. The Examiner, however, did not acknowledge that the '043 patent, and in particular, that the provisional application to which the '043 patent claims priority, does not disclose the range of circulating white blood cells, which has been added by the present amendments. Because the Examiner has

not addressed this distinction over the prior art, the Examiner has not established a *prima facie* case of obviousness of the present claims.

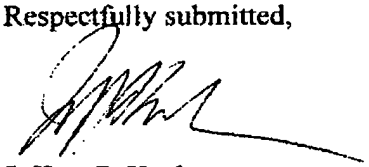
Applicants also are presently investigating inventorship issues associated with the newly amended claims, and will take corrective action, as appropriate, once that investigation has concluded.

In view of the above, Applicants respectfully request the Examiner to withdraw the present rejection over §103.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that all pending claims as currently presented are in condition for allowance. If, for any reason, the Examiner disagrees, please call the undersigned attorney at 202-736-8914 so that Applicants may attempt to resolve any matter still outstanding before issuing another action. Favorable reconsideration is respectfully requested.

Respectfully submitted,



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